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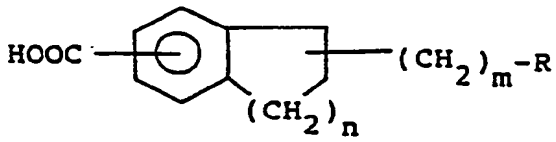
(71) Applicant: DAIICHI SEIYAKU CO. LTD.
14-10, Nihonbashi 3-chome
Chuo-ku Tokyo(JP)

(72) Inventor: Masumura, Hidemi c/o Daiichi Seiyaku Co., Ltd
14-10, Nihonbashi 3-chome Chuo-ku
Tokyo(JP)
Inventor: Sakuma, Kyoko c/o Daiichi Seiyaku Research Institute 16-13 Kitakasai 1-chome Edogawa-ku Tokyo(JP)
Inventor: Ashida, Shinichiro c/o Daiichi Seiyaku
Research Institute 16-13 Kitakasai 1-chome Edogawa-ku Tokyo(JP)

(74) Representative: Kinzebach, Werner, Dr. et al
Patentanwälte Reitstötter, Kinzebach und Partner Sternwartstrasse 4 Postfach 86 06 49
D-8000 München 86(DE)

(54) Antidiabetic agent.

(57) The invention relates to the use of a compound represented by formula (I):



(I)

wherein R represents an imidazolyl group, a thiazolyl group or a pyridyl group; n represents 1 or 2; and m represents an integer of from 1 to 4,
or a pharmaceutically acceptable salt thereof for preparing a pharmaceutical composition for treating diabetes.

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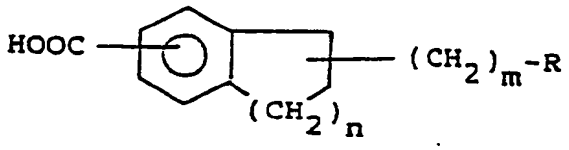
ANTIDIABETIC AGENT

FIELD OF THE INVENTION

This invention relates to an antidiabetic agent which comprises a compound represented by formula (I):



(I)

wherein R represents an imidazolyl group, a thiazolyl group or a pyridyl group; n represents 1 or 2; and m represents an integer of from 1 to 4,
or a pharmaceutically acceptable salt thereof as an active ingredient, and the use thereof for preparing an antidiabetic pharmaceutical composition.

BACKGROUND OF THE INVENTION

The compounds of formula (I) are known to inhibit the synthesis of thromboxane A_2 and have therapeutic effects on ischemic heart diseases (U.S. Patent No. 4,665,188), but unknown for its antidiabetic effects.

(E)-3-(4-(1-Imidazolylmethyl)phenyl)propenoic acid hydrochloride is known to inhibit the synthesis of thromboxane A_2. This compound was orally administered to diabetic test animals, however, the effect obtained was not satisfactory for the treatment (Abstract of the 27th Congress of the Japanese Society of Nephrology 196, (1984)).

SUMMARY OF THE INVENTION

The inventors have conducted extensive research to find out compounds having antidiabetic effects. As a result, it has now been found that the compounds represented by formula (I) exhibit the above-described effects, thus reaching the present invention.

This invention relates to an antidiabetic agent which comprises a compound represented by formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient and to the use of a compound represented by formula (I) or a pharmaceutically acceptable salt thereof for preparing an antidiabetic pharmaceutical composition.

DETAILED DESCRIPTION OF THE INVENTION

Pharmaceutically acceptable salts of the compound of formula (I) include acid addition salts formed with inorganic acids, e.g., hydrochloric acid, sulfuric acid, nitric acid, etc., or organic acids, e.g., fumaric acid, tartaric acid, maleic acid, succinic acid, oxalic acid, etc., and salts formed from a carboxyl group and an alkali metal, e.g., sodium, potassium, etc., or an alkaline earth metal, e.g., calcium, magnesium, etc.

The compounds of formula (I) and salts thereof proved highly safe on examination of acute toxicity (LD50) in oral administration or intravenous injection to rats.

The compound of formula (I) or. a salt thereof can be formulated into various pharmaceutical preparations, such as tablets, powders, capsules, and injectable solutions, according to known pharmaceutical techniques and is usually administered orally or intravenously.

The dose level of the compound of formula (I) or a salt thereof generally ranges from 50 to 1000

mg/day for adult (body weight: about 50 to 60 kg) in oral administration.

The compound of formula (I) or a salt thereof experimentally exhibited excellent antidiabetic effects such as, hypoglycemic activity and improvement of glucose tolerance in a diabetic model such as streptozotocin-induced diabetic spontaneous hypertensive rats, and also exhibited no significant side effect in case of long term oral administration. Therefore, the compound of formula (I) or a salt thereof is useful as an diabetic agent.

The present invention is now illustrated in greater detail with reference to the following Test Example and Reference Example, but it should be understood that the present invention is not limited thereto.

TEST EXAMPLE 1

Efficacy in Diabetic Model

Test Animal:

5-Week old spontaneous hypertensive male rats (SHR), available from Nippon Charles River, were used. Streptozotocin (STZ) was dissolved in a 0.1M citrate buffer solution (pH 4.5) and injected to the tail vein of the rats at a dose level of 50 mg/kg to prepare diabetic rats. For control, rats received 1 ml/kg of the citrate buffer solution alone through administration, to the tail vein. After one week from the STZ administration, blood was taken from the tail vein of the unanesthetized rats, and the blood sugar level was determined. Those rats having a blood sugar level of 300 mg/dl or higher were used as diabetic rats.

Administration of Drug:

6-(1-Imidazolylmethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid hydrochloride hemihydrate hereinafter referred to as Compound A) was dissolved in distilled water and administered orally to the test animals at a dose level of 1 mg/kg/day or 10 mg/kg/day for consecutive 5 months from one week after the administration of STZ or a citrate buffer solution.

Determination of Blood Sugar Level

Just before the administration of Compound A, blood was sampled from the tail vein of the rats without any restriction of diet to determine the blood sugar level using a commercial glucose assay kit (Trade name: New Blood Sugar Test, produced by Boehringer Mannheim Co., Ltd., West Germany). The result was shown in Table 1, as expressed as mean ± S.E..

Determination of Glucose Tolerance

After 3 months from the start of the administration of Compound A, the rats were fasted for 18 hours. Glucose was administered orally to the rats at a dose level of 2 g/kg. Blood was sampled from the tail vein of the rats just before the administration of glucose, at 1 hour and 2 hours after the administration to determine the blood sugar level using the above method. The result was shown in Table 2, as expressed as mean ± S.E..

Result

Table 1

Hypoglycemic Activity				
	Administration Term (weeks)	Blood Sugar Level (mg/dl)		
		Dosage of Compound A (mg/kg/day)		
		0	1	10
SHR (n = 8)	0	103.8 ± 2.5	100.7 ± 1.6	108.0 ± 3.2
	2	96.6 ± 2.6	95.4 ± 2.8	90.9 ± 1.5
	8	94.2 ± 1.5	94.5 ± 1.5	93.2 ± 1.8
Diabetic SHR(n = 7)	0	356.1 ± 9.6	374.6 ± 17.3	361.4 ± 10.6
	2	481.5 ± 36.4	406.3 ± 39.9	365.2 ± 40.9*
	8	544.2 ± 30.0	445.0 ± 57.6	277.3 ± 44.7**
n: Number of test animals				

*: P<0.05 compared with the control group (not administered Compound A)
**: P<0.01 Compared with the control group

As apparently from Table 1, Compound A exhibited a tendency to lower the high blood sugar level of the diabetic SHR from 2 weeks after the start of the administration of Compound A, and lowered significantly the blood sugar level at 8 weeks after the start of the administration of Compound A. However, the blood sugar level in SHR was not affected by the administration of Compound A. Therefore, it was confirmed that Compound A lowered the high blood sugar level in diabetic animals.

Table 2

Effect on Glucose Tolerance			
Sampling Time	Blood Sugar Level (mg/dl)		
	Dosage of Compound A (mg/kg/day)		
	0 (n = 7)	1 (n = 7)	10 (n = 8)
Just Before the Glucose load	178.5 ± 32.8	136.8 ± 19.0	105.1 ± 5.7
1 Hour after Glucose load	329.5 ± 34.9	255.4 ± 19.7	202.4 ± 15.7*
2 Hour after Glucose load	280.8 ± 41.9	167.3 ± 17.5	137.1 ± 5.9

*: P<0.05 compared with the control group

As apparently from Table 2, Compound A improved the glucose torelance in the diabetic SHR.

TEST EXAMPLE 2

Acute toxicities of Compund A in rats through oral administration or intravenous injection were as follows.

TABLE 3

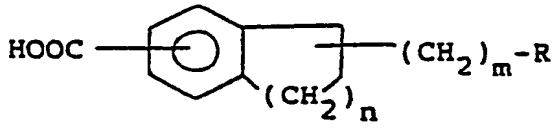
Acute Toxicity in Rats		
LD_{50} (mg/kg)		
Male	Female	
2438	1994	(p.o.)
807	783	(i.v.)
Reference Example		
Compound A	20 mg	
Lactose	50 mg	
Corn Starch	25.5 mg	
Hydroxypropyl Cellulose	4 mg	
Magnesium Stearate	0.5 mg	
Total	100 mg per one tablet	

According to the above formulation, the tablet containing Compound A was prepared by usual pharmaceutical techniques.

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

Claims

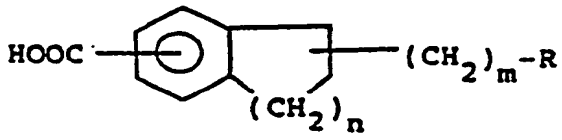
1. An antidiabetic agent which comprises a compound represented by formula (I):



(I)

wherein R represents an imidazolyl group, a thiazolyl group or a pyridyl group; n represents 1 or 2; and m represents an integer of from 1 to 4,
or a pharmaceutically acceptable salt thereof as an active ingredient.

2. The use of a compound represented by formula (I):



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01.08.90 Bulletin 90/31

(71) Applicant: **DAIICHI SEIYAKU CO. LTD.**
14-10, Nihonbashi 3-chome
Chuo-ku Tokyo 103(JP)

(72) Inventor: **Masumura, Hidemi c/o Daiichi Seiyaku Co., Ltd**
14-10, Nihonbashi 3-chome Chuo-ku Tokyo(JP)
Inventor: **Sakuma, Kyoko c/o Daiichi Seiyaku Research Institute 16-13 Kitakasai 1-chome Edogawa-ku Tokyo(JP)**
Inventor: **Ashida, Shinichiro c/o Daiichi Seiyaku**
Research Institute 16-13 Kitakasai 1-chome Edogawa-ku Tokyo(JP)

(74) Representative: **Kinzebach, Werner, Dr. et al**
Patentanwälte Reitstötter, Kinzebach und Partner Sternwartstrasse 4 Postfach 86 06 49
D-8000 München 86(DE)

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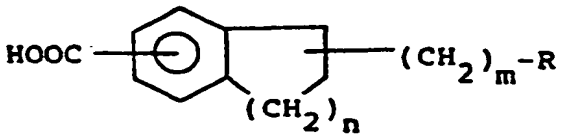

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PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number

EP 88 11 0813

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,A	US-A-4 665 188 (MUNEFUMI KANAO) * Column 1; claims * --	1,2	A 61 K 31/415 A 61 K 31/425 A 61 K 31/44
A	THE LANCET, June 16, 1984, pages 1322-1325; A.H. BARNETT et al.: "Specific thromboxane synthetase inhibition and albumin excretion rate in insulin-dependent diabetes" * The whole article * ----	1,2	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely:

Claims searched incompletely: 1,2

Claims not searched:

Reason for the limitation of the search:

The positions of the substituents in the Markush formula of claims 1 and 2 allow too many variables and therefore make a complete search not feasible. The pharmacological activity of the compounds is poorly supported by tests, i.e. only one derivative is used. (EPC Art. 84).

Place of search	Date of completion of the search	Examiner
THE HAGUE	20-04-1990	KLAVER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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